REMARKS

Claims 1-5 have been canceled. Claims 6-11 are in the case. These are all new claims. Claim 6 is now the sole independent claim.

The starting point for basis of claim 6 is claim 2 as filed.

New claim 6 has been recast compared to canceled claim 2 in reciting "screening a selective inhibitor of COX-2 for likelihood of success in treating cancer, Alzheimer's disease or atherosclerosis". Basis for this is submitted to be found in the application as filed at page 11, lines 17-19 and 22-23.

New claim 6 also differs from canceled claim 2 in reciting "the more of (a), (b), (c), (d), (e), (f) and (g) being met, the greater is the likelihood of success. Basis for this is submitted to be found in the application as filed at page 11, lines 19-21.

We turn now to basis for changes in the description of the tests (a), (b), (c), (d), (e), (f) and (g).

Tests (b), (c), (d), (e), (f) and (g) are treated herein before test (a) because the description of step (a) below is set forth with explanation.

The wording of tests (b), (c), (d), (e), (f) and (g) has been changed compared to that of canceled claim 2 in that each recites "causing". Basis for this is as follows. Test (b), application as filed at page 6, line 16; (c), application as filed at page 7, line 14; (d), application as filed at page 8, line 6; (e), application as filed at page 9, line 4; (f), application as filed at page 9, line 22; (g), application as filed at page 10, line 8.

We turn now to test (a) of new claim 6.

It recites "causing increase in PPRE luciferase activity by at least 100 % as manifested by at least doubling of luciferase activity based on data that have been normalized with β-galactosidase activity". Basis for this is submitted to be found in the application as filed at page 3, lines 5-8 under "Detailed Description". The term "causing" is

based on page 16, line 5. That increase is being determined is evident from the "at least doubling".

We turn now to an explanation of test (a).

Increase in PPRE activation means increase in PPAR-mediated gene transcription. See the application as filed at page 4, lines 10-11. This causes change in the expression of genes that are regulated by PPARs.

Basis for new claims 6-11 is found in working Examples IV-VIII.

We turn now to the rejections.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. Claim 1 has been canceled. Reconsideration is requested.

Claim 2a has been rejected under 35 U.S.C. 112, first paragraph, on the basis that it does not screen for a therapeutic function. In response firstly, it is noted that "function" is no longer mentioned in the claims. In response secondly, claim 6 recites what is measured for each of tests (a), (b), (c), (d), (e), (f) and (g); that is what it should do. In response thirdly, as explained above, test (a) results indicate increase in PPAR-mediated gene expression. Literature indicates increases in PPAR activation may benefit patients with Alzheimer's disease and atherosclerosis. Some literature indicates that increase in PPAR activation may benefit those with cancer while other literature indicates that increase in PPAR activation may not benefit those with cancer; it is submitted that this is sufficient for a screening test where at least two parameters must be met. Reconsideration of the rejection is requested.

Claim 2 is rejected under 35 U.S.C. 101 on the basis of lacking patentable utility. Claim 2 has been canceled. New claim 6 names its utility as screening a selective inhibitor of COX-2 for likelihood of success in treating a patient having or at risk for cancer, Alzheimer's disease or atherosclerosis. It is submitted that *in vitro screening* utility is important in the drug industry in providing basis for selection of drugs to test on animals and then on humans.

Reconsideration is requested.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Winde et al (Cancer Letters 1998). Claim 1 has been canceled. Reconsideration is requested.

As an aside, it is noted that the rejection depends on sulindac being a selective inhibitor of COX-2. The rejection relies on Lemoult for sulindac being a selective inhibitor of COX-2. Lemoult is a press release and not a scientific article. Its statement that sulindac is a selective inhibitor of COX-2 is flat out wrong. Data on sulindac is provided at page 460 of Fosslien, E., Clinical Devices in Clinical Laboratory Sciences 35(5), 431-502 (2000), pages 431, 459, 460, enclosed as Appendix A hereto. The data in Fosslien shows rather that sulindac is a selective inhibitor of COX-1, even more so than aspirin.

Allowance is requested.

Respectfully submitted,

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Biochemistry of Cyclooxygenase (COX)-2 Inhibitors and Molecular Pathology of COX-2 in Neoplasia

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ABSTRACT: Several types of human tumors overexpress cyclooxygenase (COX) -2 but not COX-1, and gene knockout transfection experiments demonstrate a central role of COX-2 in experimental tumorigenesis. COX-2 produces prostaglandins that inhibit apoptosis and stimulate angiogenesis and invasiveness. Selective COX-2 inhibitors reduce prostaglandin synthesis, restore apoptosis, and inhibit cancer cell proliferation. In animal studies they limit carcinogen-induced tumorigenesis. In contrast, aspirin-like nonselective NSAIDs such as sulindac and indomethacin inhibit not only the enzymatic action of the highly inducible, proinflammatory COX-2 but the constitutively expressed, cytoprotective COX-1 as well. Consequently, nonselective NSAIDs can cause platelet dysfunction, gastrointestinal ulceration, and kidney damage. For that reason, selective inhibition of COX-2 to treat neoplastic proliferation is preferable to nonselective inhibition. Selective COX-2 inhibitors, such as meloxicam, celecoxib (SC-58635), and rofecoxib (MK-0966), are NSAIDs that have been modified chemically to preferentially inhibit COX-2 but not COX-1. For instance, meloxicam inhibits the growth of cultured colon cancer cells (HCA-7 and Moser-S) that express COX-2 but has no effect on HCT-116 tumor cells that do not express COX-2. NS-398 induces apoptosis in COX-2 expressing LNCaP prostate cancer cells and, surprisingly, in colon cancer S/KS cells that does not express COX-2. This effect may due to induction of apoptosis through uncoupling of oxidative phosphorylation and down-regulation of Bcl-2, as has been demonstrated for some nonselective NSAIDs, for instance, flurbiprofen. COX-2 mRNA and COX-2 protein is constitutively expressed in the kidney, brain, spinal cord, and ductus deferens, and in the uterus during implantation. In addition, COX-2 is constitutively and dominantly expressed in the pancreatic islet cells. These findings might somewhat limit the use of presently available selective COX-2 inhibitors in cancer prevention but will probably not deter their successful application for the treatment of human cancers.

I. INTRODUCTION

There is substantial epidemiological, experimental, and clinical evidence that nonsteroidal antiinflammatory drugs (NSAIDs) possess antineoplastic properties.[1]

1040-8363/00/$.50

TABLE 4
List of Selective COX-2 Inhibitors

INHIBITOR	MANUFACTURER	TRADE NAME	REFERENCES
Celecoxib (SC-58635)	Searle/Monsanto	Celebrex	(172)(164)(168)
Rofecoxib (MK-0966)	Merck	Vioxx™	(164)(168)(329)
Meloxicam	Thomae	Mobec®	(330)(331)(164) (329)
Nimesulide	Indoco	Nimid	(329)
Flosulide	Merck		(163)
L-745,337	Boehringer Ingelheim		(163)
JTE-522	Japan Tobacco, Inc.		(212)(213)
Etodolac	Royce Laboratories		(330)(331)(329)
Diclofenac	Faulding Inc.		(330)(331)(168)
DFU	Merck		(332)
SC-58125			(204)(212)
SC-236	Searle/Monsanto		(172)(204)
NS-398			(204)(212) (333)(330)

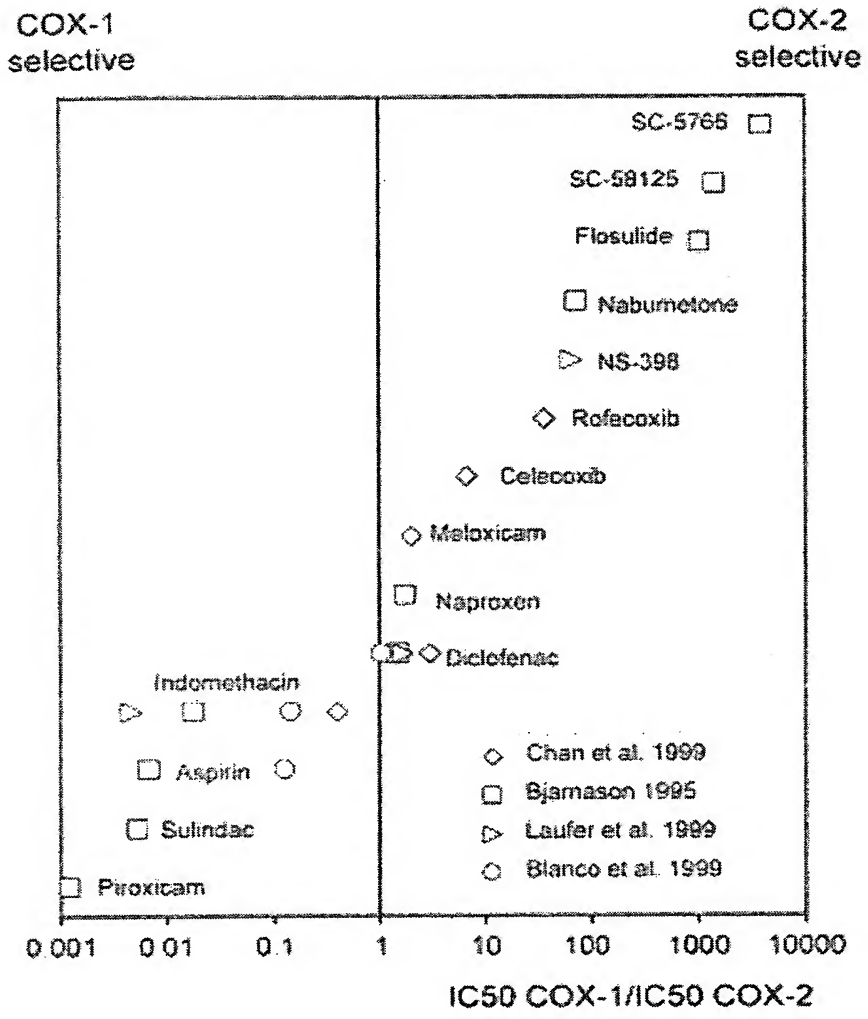

FIGURE 5. *In vitro* and *ex vivo* inhibition values (IC50) of cyclooxygenase (COX)-1 and -2 vary for different nonsteroid antiinflammatory drugs (NSAIDs) and, as shown, for instance, for indomethacin depends on the assay method used. Diagram ranks nonselective and COX-2 selective NSAIDs (right side of diagram) according to data from the five sources indicated above. Laufer *et al.*[167] used a whole blood, mononuclear cell assay with lipopolysaccharide (LPS) as the COX-2 inducer. In several cases only limited data have been published. For instance, for meloxicam, celecoxib, and rofecoxib, only data from a single source is available. Piroxicam is a strong COX-1 inhibitor. In contrast, flosulide, SC-58125, and SC-5766 inhibit COX-2 the most. However, only clinical trials can establish proof of the therapeutic significance of a selective COX-2 inhibitor. (For further detail see text.)